

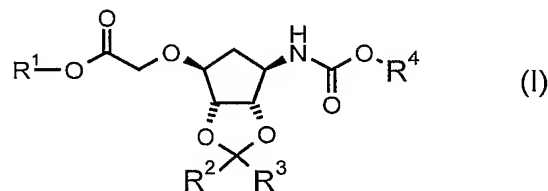
CHEMICAL PROCESS

The present invention concerns a process for the preparation of alkoxycarbonylmethoxy cyclopentanes which are useful intermediates in the preparation of pharmaceutically active triazolo[4,5-*d*]pyrimidine cyclopentanes.

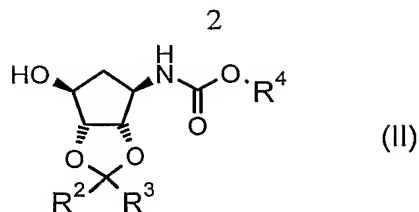
The compound [1*S*-(1 $\alpha$ , 2 $\alpha$ , 3 $\beta$  (1*S*\*, 2*R*\*), 5 $\beta$ )]-3-[7-[2-(3,4-difluorophenyl)-cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol (Compound A), and similar such compounds, are disclosed in WO 00/34283 and WO 99/05143. These compounds are disclosed as P<sub>2T</sub> (which is now usually referred to as P<sub>2Y12</sub>) receptor antagonists. Such antagonists can be used as, *inter alia*, inhibitors of platelet activation, aggregation or degranulation.

Compounds of formula (I) (see below) are useful in the preparation of Compound A (see example 1 of WO 01/92263). The preparation of a compound of formula (I) is disclosed in example 1 of WO 01/92263 and in that example the process was conducted at 0°C. It has been found that when scaling up the process of example 1 of WO 01/92263 (say to more than 0.2 mole scale) and keeping the temperature at 0°C, competing side-reactions lead to a significant increase in the level of impurities, an increase in the reagent requirement, and a resulting reduction in the percentage yield of compound of formula (I). This is clearly a problem as it makes the process more costly and less efficient. We have now unexpectedly found that when the process is operated on a 0.2 mole scale or more, the use of a lower temperature allows the compound of formula (I) to be produced in good yield and minimizes the products of the unwanted side reactions.

The present invention provides a process for the preparation of a compound of formula (I):



wherein R<sup>1</sup> is C<sub>1-6</sub> alkyl; R<sup>2</sup> and R<sup>3</sup> are, independently, C<sub>1-6</sub> alkyl; and R<sup>4</sup> is C<sub>1-6</sub> alkyl (such as *tert*-butyl) or benzyl (wherein the phenyl ring of benzyl is optionally substituted by nitro, S(O)<sub>2</sub>(C<sub>1-4</sub> alkyl), cyano, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C(O)(C<sub>1-4</sub> alkyl), N(C<sub>1-6</sub> alkyl)<sub>2</sub>, CF<sub>3</sub> or OCF<sub>3</sub>); the process comprising reacting a compound of formula (II):



wherein R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as defined above, with a suitable base; and reacting the product so formed with R<sup>1</sup>OC(O)CH<sub>2</sub>X, wherein R<sup>1</sup> is as defined above and X is chloro, bromo or iodo; wherein the process is carried out in a suitable solvent at a temperature in the range  
 5 -40°C to -5°C; and wherein at least 0.2 moles of the compound of formula (II) are used in the process.

Alkyl groups and moieties are straight or branched chain and comprise, for example, 1 to 6 (such as 1 to 4) carbon atoms. Examples of alkyl groups are methyl, ethyl, n-propyl, iso-propyl or tert-butyl.

10 In one particular aspect the present invention provides a process wherein R<sup>1</sup> is C<sub>1-4</sub> alkyl (for example ethyl).

In another aspect the present invention provides a process wherein R<sup>2</sup> and R<sup>3</sup> are, independently, C<sub>1-4</sub> alkyl; for example R<sup>2</sup> and R<sup>3</sup> are both methyl.

15 In a further aspect of the invention R<sup>4</sup> is benzyl (wherein the phenyl ring of benzyl is optionally substituted by C<sub>1-4</sub> alkyl); for example R<sup>4</sup> is unsubstituted benzyl.

In a still further aspect the present invention provides a process wherein X is bromo.

Suitable bases include an alkali metal C<sub>1-6</sub> alkoxide (for example potassium tert-butoxide).

20 In another aspect of the invention the molar ratio of suitable base: R<sup>1</sup>O<sub>2</sub>CCH<sub>2</sub>X : compound of formula (II) is (1 to 1.3):(1 to 1.3):1, for example (1.1 to 1.3):(1.1 to 1.3):1, such as about 1.2:1.2:1.

Suitable solvents include cyclic and aliphatic ethers (such as tetrahydrofuran, diethyl ether, diisopropyl ether or methyl tert-butyl ether) and aromatic solvents (such as benzene, toluene or a xylene). The solvent can be a mixture of two or more solvents (for example a  
 25 mixture of an ether and an aromatic solvent, as exemplified above). In another aspect the invention provides a process wherein an ether, as exemplified above, is used as solvent.

In yet another aspect of the invention the temperature is in the range -30°C to -10°C, for example -25°C to -15°C.

30 In a further aspect the process of the present invention comprises adding a solution of suitable base to a solution of a compound of formula (II) at -15 to -25°C, and then adding to

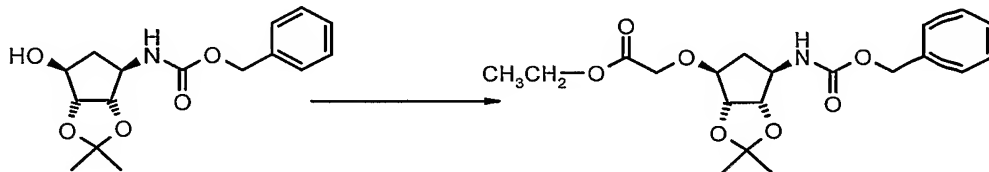
this mixture a solution of  $R^1OC(O)CH_2X$  at  $-15$  to  $-25^\circ\text{C}$ , a suitable ether being used as solvent.

A compound of formula (II) can be prepared by a method, or a method analogous to a method, disclosed in the literature (for example WO 01/92263).

5 The following Example illustrates the invention.

### EXAMPLE 1

This Example illustrates a process for the preparation of [3aS-(3 $\alpha$ ,4 $\alpha$ ,6 $\alpha$ ,6 $\alpha$ )]-[2,2-dimethyl-6-((ethoxycarbonyl)methoxy)-tetrahydro-4H-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester.



A solution (Solution A) of [3aS-(3 $\alpha$ ,4 $\alpha$ ,6 $\alpha$ ,6 $\alpha$ )]-[tetrahydro-6-hydroxy-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester (80g, 260 mmol) in THF (160ml), under a nitrogen atmosphere, was cooled to  $-22^\circ\text{C}$ . A solution of potassium tert-butoxide (36.1g, 312 mmol) in THF was prepared and added to the cooled Solution A over a period of 30 minutes, while maintaining the reaction temperature at about  $-20^\circ\text{C}$ . This provided a reaction mixture.

A pre-made solution of ethyl bromoacetate (53.2g, 312 mmol) in THF was then added to the reaction mixture over a period of 30 minutes while maintaining the reaction temperature at about  $-20^\circ\text{C}$ . The resulting mixture was stirred for approximately an hour at  $-22^\circ\text{C}$ . HPLC analysis showed that there was a 98% conversion to the desired product.

Table below shows variations on this process.

Ex	Mole ratios of reagents to (II)		<u>t-BuOK</u> Addition		<u>EtBrAc</u> Addition		<u>Hold time</u> (min.)
	t-BuOK	EtBrAc	<u>Time</u> (min.)	<u>Temp.</u> ( $^\circ\text{C}$ )	<u>Time</u> (min.)	<u>Temp.</u> ( $^\circ\text{C}$ )	
2	1.40	1.46	13	-20	34	-20	23
3	1.15	1.15	22	-22	42	-22	20

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Ex	Mole ratios of reagents to (II)		<u>t-BuOK</u> <u>Addition</u>		<u>EtBrAc</u> <u>Addition</u>		<u>Hold time</u> <u>(min.)</u>
	t-BuOK	EtBrAc	<u>Time</u> <u>(min.)</u>	<u>Temp.</u> <u>(°C)</u>	<u>Time</u> <u>(min.)</u>	<u>Temp.</u> <u>(°C)</u>	
4	1.20	1.20	30	-20	45	-20	15
5	1.10	1.10	20	-30	30	-30	20
6	1.20	1.20	20	-22	30	-22	20
7	1.10	1.10	20	-10	30	-10	20
8*	1.20	1.20	20	-22	30	-22	20
9	1.20	1.20	30	-22	180	-22	150
10	1.20	1.20	25	-21	45	-21	10
11	1.20	1.20	30	-22	40	-20	10
12	1.2	1.2	13	-23/-28	10	-22/-28	30
13	1.15	1.15	12	-20/-22	15	-19/-24	30

Ex = Example number

(II) = [3aS-(3α,4α,6α,6α)]-[tetrahydro-6-hydroxy-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester

5 t-BuOK = potassium tert-butoxide

EtBrAc = ethyl bromoacetate

\* = Both the THF solution of compound of formula (II) and potassium *tert*-butoxide were filtered before use